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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/763,955	02/28/2001	Reld W. Von Borstel	1331-334	3848

23117 7590 04/21/2008
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EXAMINER	
LEWIS, PATRICK T	

ART UNIT	PAPER NUMBER
1623	

MAIL DATE	DELIVERY MODE
04/21/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/763,955	VON BORSTEL, RELD W.	
	Examiner	Art Unit	
	Patrick T. Lewis	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48-50,55,62-64 and 68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48-50,55,62-64 and 68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11152007; 09142007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I in the reply filed on July 21, 2003 is acknowledged. The requirement was made FINAL in the Office Action dated September 9, 2004.

Applicant's Response Dated January 28, 2008

2. Claims 48-50, 55, 62-64 and 68 are pending. An action on the merits of claims 48-59 and 62-68 is contained herein below.

3. The provisional rejection of claim 55 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 31-32 and 38-41 of copending Application No. 09/930,494 is maintained for the reasons of record as set forth in the Office Action dated July 27, 2007.

4. The rejection of claims 48-50, 55, 62-64 and 68 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained for the reasons of record as set forth in the Office Action dated July 27, 2007.

Rejections of Record Set Forth in the Office Action Dated August 9, 2006

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. Claim 55 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 31-32 and 38-41 of copending Application No. 09/930,494.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

7. Applicant has failed to set forth arguments as to why the provisional rejection is improper.

8. Claims 48-50, 55, 62-64 and 68 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant specification invites the skilled artisan to unduly experiment. Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below as seen in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). A conclusion of lack of enablement means that, based on the evidence regarding each of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

The factors include, but are not limited to:

1. The breadth of the claims,
2. The nature of the invention,
3. The state of the prior art,

4. The level of one of ordinary skill,
5. The level of predictability in the art,
6. The amount of direction provided by the inventor,
7. The existence of working examples, and
8. The quantity of experimentation needed to make and/or use the invention based on the content of the disclosure.

Breath of Claims

Claims 48-50, 55, 62-64 and 68 are drawn to a method for treating congenital mitochondrial diseases.

Nature of Invention

This invention relates generally to compounds and methods for treatment and prevention of diseases, developmental delays, and symptoms related to mitochondrial dysfunction. Pyrimidine nucleotide precursors are administered to a mammal, including a human, for the purpose of compensating for mitochondrial dysfunction and for improving mitochondrial functions. It is an object of this invention to provide a practical treatment for mitochondrial diseases that is beneficial in the case of mitochondrial electron transport chain deficits regardless of the specific molecular defects.

State of the Prior Art

At the time of the invention, the treatment of mitochondrial disorders was ineffective. There were no correlations between treatment regimens and therapeutic responses to disorders. Treatment was unpredictable and heterogenous. The examiner directs applicant to PRZYREMBEL *J. Inher. Metab. Dis.* (1987), Vol. 10, pages 129-146 (PRZYREMBEL). PRZYREMBEL teaches, “Mitochondrial disorders,

namely defects of fatty acid oxidation, defects of pyruvate metabolism and defects of the respiratory chain are heterogenous in clinical picture and in response to therapeutic attempts. Defects of fatty acid metabolism are amenable to therapy by dietary means, carnitine substitution and in some cases with vitamins. Defects in pyruvate metabolism do not respond to therapy except in some special cases. Therapeutic attempts include dietary measures, vitamins as coenzyme precursors. Defects in the respiratory chain appear to respond to treatment only in exceptional cases. Evaluation of treatment effects appears to be singularly difficult." See Abstract.

Level of Ordinary Skill in the Art

The level of ordinary skill in the art is seen to be a M.D. specializing in mitochondrial disorders or a PhD in the field of biomedical research.

Level of Predictability in the Art /Amount of Direction Provided by the Inventor

Please note that a single embodiment may provide broad enablement in cases involving predictable factors, but more is required in cases involving unpredictable factors, such as chemical or physiological activity, see *Ex. parte Hitzeman*, 9 USPQ2d 1821. The working examples in the specification are limited to the use of triacetyluridine for treating mitochondrial disorders. One of ordinary skill in the art at the time of the instant invention would have predicted that no single compound or family of compounds would have been effective for the treatment of the broad spectrums of mitochondrial disorders instantly claimed. Additionally, due to the extreme difficulty in treating mitochondrial disorders, one of ordinary skill would have set a very high bar in accessing whether treatment was successful. PRZYREMBEL teaches, "Patients with

defects in mitochondrial function are difficult to treat with our available means. When treatment is considered it has to start early and should be aggressive and run parallel to diagnostic procedures on an experimental basis…Defects in the respiratory chain appear to respond to treatment only in exceptional cases. Evaluation of treatment effects appears to be singularly difficult."

In addition to the teachings of PRZYREMBEL, as set forth supra, the specification teaches, "while useful in isolated cases, no such metabolic cofactors or vitamins have been shown to have general utility in clinical practice in treating mitochondrial diseases. Similarly, dichloracetic acid (DCA) has been used to treat mitochondrial cytopathies such as MELAS; DCA inhibits lactate formation and is primarily useful in cases of mitochondrial diseases where excessive lactate accumulation itself is contributing to symptoms. However, DCA does not address symptoms related to mitochondrial insufficiency per se and can be toxic to some patients, depending on the underlying molecular defects…Mitochondrial diseases comprise disorders caused by a huge variety of molecular lesions or defects, with the phenotypic expression of disease further complicated by stochastic distributions of defective mitochondria in different tissues." See pages 2-3 of the specification.

Working Examples / Quantity of Experimentation Needed to make and/or use the Invention Based on the Content of the Disclosure

The working examples on pages 40-49 have been noted. The examples are limited to the use of triacetyluridine. Example 3 is directed to the treatment of renal tubular acidosis. The subject (2 year-old girl) had Leigh's Syndrome; however, the

example does not suggest the efficacious treatment of Leigh's Disease. Example 8 is directed to the therapeutic effect of triacetyluridine in the 3-nitropropionic acid model of Huntington's disease. These examples are not be sufficient to support applicant's claim of the treatment of the instantly claimed disorders. PRZYREMBEL teaches, "Therefore recommendations about what to do with an individual patient with a specific defect will be relatively vague. Evaluation of the effect of any chosen treatment regimen is also problematic. Many mitochondrial encephalomyopathies tend to show an episodic course. Acute attacks, leading to neurological deficits, and spontaneous recovery follow each other. Recovery, however, is in most cases only partial and a progressive downhill course is the result." See pages 129-130.

9. Applicant's arguments filed January 28, 2008 have been fully considered but they are not persuasive. Applicant argues that (1) the pending claims were not rejected in a prior Office Action and (2) Przyrembel is not representative of the state of the art and contends DiMauro teaches "enormous progress" has been made.

Applicant's arguments are not persuasive. In regards to applicant's first argument, a rejection can be made at any point during prosecution. The Office Action mailed on July 27, 2007 was not a FINAL Office Action; thus, applicant has been given an opportunity to respond to all issues raised by the examiner. Applicant's argument regarding DiMauro has been noted; however, "enormous progress" does not equate to successful treatment. There is nothing in DiMauro which suggests the instant method is enabled. Furthermore, applicant should also note that the application must be enabled at the time of filing. Whether the specification would have been enabling as of the filing

date involves consideration of the nature of the invention, the state of the prior art, and the level of skill in the art. The state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date. Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing. In general, if an applicant seeks to use a publication to prove the state of the art for the purpose of the enablement requirement, the publication must have been published (made available to the public) earlier than the effective filing date of the application.

Conclusion

10. Claims 48-50, 55, 62-64 and 68 are pending. Claims 48-50, 55, 62-64 and 68 are rejected. No claims are allowed.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Contacts

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick T. Lewis whose telephone number is 571-272-0655. The examiner can normally be reached on Monday - Friday 10 am to 3 pm (Maxi Flex).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Dr. Patrick T. Lewis/
Primary Examiner, Art Unit 1623

ptl